

### AMENDMENTS TO THE CLAIMS

1. (Currently Amended) A method of treatment, comprising:  
identifying a human patient that is susceptible to ischemia; and  
reducing the likelihood of an occurrence of a harmful effect of ischemia by administering an effective sufficient amount of a stable free radical nitroxide to prevent a harmful effect of ischemia in the human patient prior to the onset of ischemia;  
wherein the likelihood is reduced in comparison to a human patient who was not subjected to the administering step.
2. (Original) The method of Claim 1, wherein the nitroxide is 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl.
3. (Original) The method of Claim 1, wherein the human patient's susceptibility to ischemia arises from a medical procedure associated with a significant ischemic risk.
4. (Original) The method of Claim 3, wherein the medical procedure is the treatment of a hemorrhage.
5. (Original) The method of Claim 3, wherein the medical procedure is the treatment of an aneurysm.
6. (Currently Amended) The method of Claim ~~[[5]]~~ 3, wherein the medical procedure is surgery.
7. (Currently Amended) The method of Claim ~~[[5]]~~ 3, wherein the medical procedure is an endovascular procedure.
8. (Original) The method of Claim 1, wherein the mode of nitroxide administration is selected from the group consisting of oral and intravenous administration.
9. (Currently amended) A method of treatment comprising:  
identifying a patient scheduled to undergo a medical procedure involving a ~~significant~~ risk of ischemia;  
reducing the likelihood of an occurrence of a harmful effect of ischemia by administering to the patient, prior to the medical procedure, an effective prophylactic amount of a stable free radical nitroxide;  
performing the medical procedure; and

administering to the patient, an additional prophylactic or therapeutic amount of a stable free radical nitroxide to ameliorate a harmful effect of ischemia.

10. (Original) The method of Claim 9, wherein the nitroxide is 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl.

11. (Original) The method of Claim 9, wherein the medical procedure is the treatment of a hemorrhage.

12. (Original) The method of Claim 9, wherein the medical procedure is the treatment of an aneurysm.

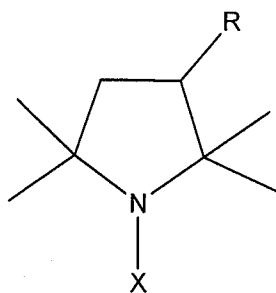
13. (Original) The method of Claim 9, wherein the medical procedure is surgery.

14. (Original) The method of Claim 9, wherein the medical procedure is an endovascular procedure.

15. (Original) The method of Claim 9, wherein the mode of nitroxide administration is selected from the group consisting of oral and intravenous administration.

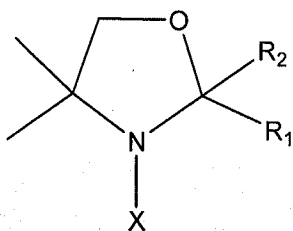
16-31 (Canceled)

32. (Currently Amended) The method of Claim 1 wherein the nitroxide is selected from the group consisting of



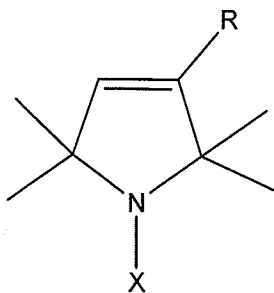
or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH, and R is selected from COOH, CONH, CN, and CH<sub>2</sub> NH<sub>2</sub>;



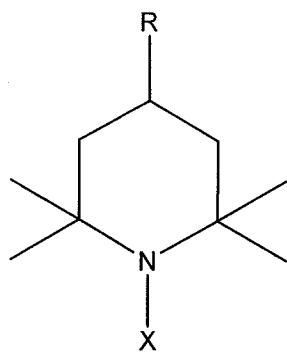
or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH, and R<sub>1</sub> is selected from CH<sub>3</sub> and spirocyclohexyl, and R<sub>2</sub> is selected from C<sub>2</sub>H<sub>5</sub> and spirocyclohexyl;



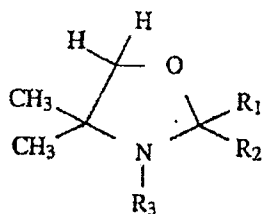
or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH and R is CONH;



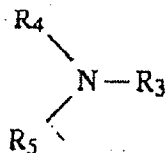
or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH and R is H, OH, and NH<sub>2</sub>;



wherein R<sub>1</sub> is -CH<sub>3</sub>; R<sub>2</sub> is -C<sub>2</sub>H<sub>5</sub>, -C<sub>3</sub>H<sub>7</sub>, -C<sub>3</sub>H<sub>7</sub>, -C<sub>4</sub>H<sub>9</sub>, -C<sub>5</sub>H<sub>11</sub>, -C<sub>6</sub>H<sub>13</sub>, -CH<sub>2</sub>-CH(CH<sub>3</sub>)<sub>2</sub>, -CHCH<sub>3</sub>C<sub>2</sub>H<sub>5</sub>, or -(CH<sub>2</sub>)<sub>7</sub>-CH<sub>3</sub>, or wherein R<sub>1</sub> and R<sub>2</sub> together form spirocyclopentane,

spirocyclohexane, spirocycloheptane, spirocyclooctane, 5-cholestane, or norbornane;  $R_3$  is - O· or - OH, or a physiologically acceptable salt thereof which has antioxidant activity;



wherein  $R_3$  is - O· or -OH; and

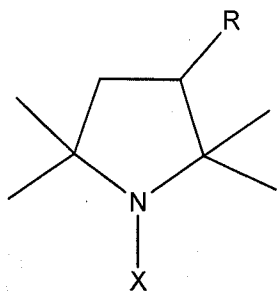
wherein  $R_4$  and  $R_5$  combine together with the nitrogen to form a heterocyclic group; wherein the atoms in the heterocyclic group (other than the N atom shown in the formula) may be all C atoms or may be C atoms and one or more N, O and/or S atoms; or

wherein  $R_4$  and  $R_5$  combine together to form substituted or unsubstituted pyrrole, imidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, pyridine, pyrimidine, or purine; or

wherein  $R_4$  and  $R_5$  themselves comprise a substituted or unsubstituted cyclic or heterocyclic group;

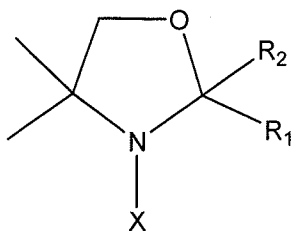
2-ethyl-2,5,5-trimethyl-3-oxazolidine-1-oxyl, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPOL), 4-amino-2,2,6,6-tetramethyl-1-piperidinyloxy (Tempamine), 3-Aminomethyl-PROXYL, 3-Cyano-PROXYL, 3-Carbamoyl-PROXYL, 3-Carboxy-PROXYL, 4-oxo-TEMPO, 4-amino-TEMPO, 4-(2-bromoacetamido)-TEMPO, 4-(ethoxyfluorophosphonyloxy)-TEMPO, 4-hydroxy-TEMPO, 4-(2-iodoacetamido)-TEMPO, 4-isothiocyanato-TEMPO, 4-maleimido-TEMPO, 4-(4-nitrobenzoyloxy)-TEMPO, and 4-phosphonoxy-TEMPO.

33. (Previously Presented) The method of Claim 9 wherein the nitroxide is selected from the group consisting of



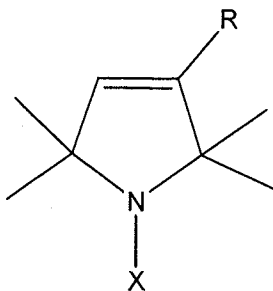
or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH, and R is selected from COOH, CONH, CN, and CH<sub>2</sub> NH<sub>2</sub>;



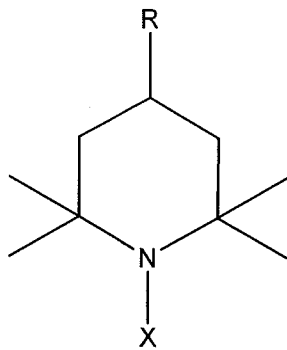
or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH, and R<sub>1</sub> is selected from CH<sub>3</sub> and spirocyclohexyl, and R<sub>2</sub> is selected from C<sub>2</sub> H<sub>5</sub> and spirocyclohexyl;



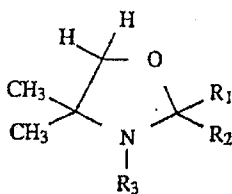
or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH and R is CONH;

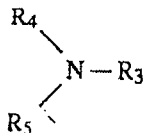


or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH and R is selected from H, OH, and NH<sub>2</sub>;



wherein  $R_1$  is  $-\text{CH}_3$ ;  $R_2$  is  $-\text{C}_2\text{H}_5$ ,  $-\text{C}_3\text{H}_7$ ,  $-\text{C}_4\text{H}_9$ ,  $-\text{C}_5\text{H}_{11}$ ,  $-\text{C}_6\text{H}_{13}$ ,  $-\text{CH}_2\text{-CH}(\text{CH}_3)_2$ ,  $-\text{CHCH}_3\text{C}_2\text{H}_5$ , or  $-(\text{CH}_2)_7\text{-CH}_3$ , or wherein  $R_1$  and  $R_2$  together form spirocyclopentane, spirocyclohexane, spirocycloheptane, spirocyclooctane, 5-cholestane, or norbornane;  $R_3$  is  $-\text{O}\cdot$  or  $-\text{OH}$ , or a physiologically acceptable salt thereof which has antioxidant activity;



wherein  $R_3$  is  $-\text{O}\cdot$  or  $-\text{OH}$ ; and

wherein  $R_4$  and  $R_5$  combine together with the nitrogen to form a heterocyclic group; wherein the atoms in the heterocyclic group (other than the N atom shown in the formula) may be all C atoms or may be C atoms and one or more N, O and/or S atoms; or

wherein  $R_4$  and  $R_5$  combine together to form substituted or unsubstituted pyrrole, imidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, pyridine, pyrimidine, or purine; or

wherein  $R_4$  and  $R_5$  themselves comprise a substituted or unsubstituted cyclic or heterocyclic group;

2-ethyl-2,5,5-trimethyl-3-oxazolidine-1-oxyl, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPOL), 4-amino-2,2,6,6-tetramethyl-1-piperidinyloxy (Tempamine), 3-Aminomethyl-PROXYL, 3-Cyano-PROXYL, 3-Carbamoyl-PROXYL, 3-Carboxy-PROXYL, 4-oxo-TEMPO, 4-amino-TEMPO, 4-(2-bromoacetamido)-TEMPO, 4-(ethoxyfluorophosphonyloxy)-TEMPO, 4-hydroxy-TEMPO, 4-(2-iodoacetamido)-TEMPO, 4-isothiocyanato-TEMPO, 4-maleimido-TEMPO, 4-(4-nitrobenzoyloxy)-TEMPO, and 4-phosphonoxy-TEMPO.

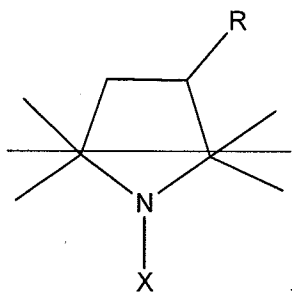
34. (Currently amended) A method of treatment comprising:

identifying a human patient that who is susceptible to ischemia associated with a medical procedure; and

reducing a harmful effect of ischemia in the human patient after the medical procedure by administering an effective amount of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl prior to the onset of ischemia and prior to the medical procedure

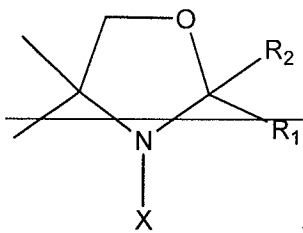
~~administering a sufficient amount of a nitroxide to reduce a harmful effect of ischemia in the human patient prior to the onset of ischemia;~~

~~wherein the nitroxide is selected from the group consisting of~~



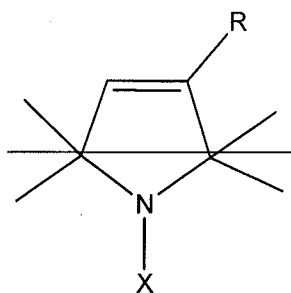
~~or a pharmaceutically acceptable salt thereof~~

~~wherein X is selected from O• and OH, and R is selected from COOH, CONH, CN, and CH<sub>2</sub>NH<sub>2</sub>;~~



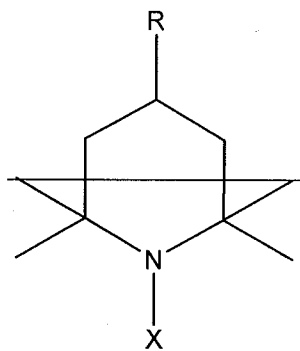
~~or a pharmaceutically acceptable salt thereof~~

~~wherein X is selected from O• and OH, and R<sub>1</sub> is selected from CH<sub>3</sub> and spirocyclohexyl, and R<sub>2</sub> is selected from C<sub>2</sub>H<sub>5</sub> and spirocyclohexyl;~~



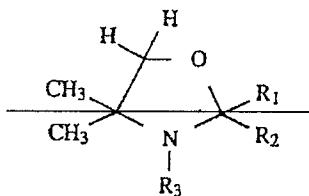
or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH and R is CONH<sub>2</sub>;



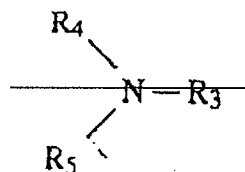
or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH and R is selected from H, OH, and NH<sub>2</sub>;



wherein R<sub>1</sub> is CH<sub>3</sub>; R<sub>2</sub> is C<sub>2</sub>H<sub>5</sub>, C<sub>3</sub>H<sub>7</sub>, C<sub>4</sub>H<sub>9</sub>, C<sub>5</sub>H<sub>11</sub>, C<sub>6</sub>H<sub>13</sub>, CH<sub>2</sub>-CH(CH<sub>3</sub>)<sub>2</sub>, CHCH<sub>3</sub>C<sub>2</sub>H<sub>5</sub>, or (CH<sub>2</sub>)<sub>7</sub>-CH<sub>3</sub>, or wherein R<sub>1</sub> and R<sub>2</sub> together form spirocyclopentane, spirocyclohexane, spirocycloheptane, spirocyclooctane, 5-cholestane, or norbornane; R<sub>3</sub> is O• or OH, or a physiologically acceptable salt thereof which has antioxidant activity;





wherein  $R_3$  is  $O\cdot$  or  $OH\cdot$ ; and

wherein  $R_4$  and  $R_5$  combine together with the nitrogen to form a heterocyclic group; wherein the atoms in the heterocyclic group (other than the N atom shown in the formula) may be all C atoms or may be C atoms and one or more N, O and/or S atoms; or

wherein  $R_4$  and  $R_5$  combine together to form substituted or unsubstituted pyrrole, imidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, pyridine, pyrimidine, or purine; or

wherein  $R_4$  and  $R_5$  themselves comprise a substituted or unsubstituted cyclic or heterocyclic group;

~~2-ethyl 2,5,5-trimethyl 3-oxazolidine-1-oxyl, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPOL), 4-amino-2,2,6,6-tetramethyl-1-piperidinyloxy (Tempamine), 3-Aminomethyl PROXYL, 3-Cyano PROXYL, 3-Carbamoyl PROXYL, 3-Carboxy PROXYL, 4-oxo-TEMPO, 4-amino-TEMPO, 4-(2-bromoacetamido)-TEMPO, 4-(ethoxyfluorophosphonyloxy)-TEMPO, 4-hydroxy-TEMPO, 4-(2-iodoacetamido)-TEMPO, 4-isothiocyanato-TEMPO, 4-maleimido-TEMPO, 4-(4-nitrobenzoyloxy)-TEMPO, and 4-phosphonoxy-TEMPO.~~

35. (Canceled) The method of Claim 34, wherein the nitroxide is 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl.

36. (Previously Presented) The method of Claim 34, wherein the human patient's susceptibility to ischemia arises from a medical procedure associated with a significant ischemic risk.

37. (Currently Amended) The method of Claim ~~[[36]]~~34, wherein the medical procedure is the treatment of a hemorrhage.

38. (Currently Amended) The method of Claim ~~[[36]]~~34, wherein the medical procedure is the treatment of an aneurysm.

39. (Currently Amended) The method of Claim ~~[[36]]~~34, wherein the medical procedure is surgery.

40. (Currently Amended) The method of Claim ~~[[36]]~~34, wherein the medical procedure is an endovascular procedure.

41. (Previously Presented) The method of Claim 34, wherein the mode of nitroxide administration is selected from the group consisting of oral and intravenous administration.

42. (Currently Amended) A method of treatment comprising:

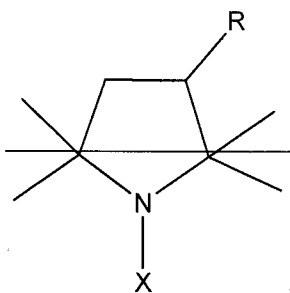
identifying a patient scheduled to undergo a medical procedure involving a significant risk of ischemia;

reducing a harmful effect of ischemia in the human patient after the medical procedure by administering an effective amount of 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl ~~administering to the patient, prior to the medical procedure, a sufficient amount of a nitroxide to reduce a harmful effect of ischemia in the human patient;~~

performing the medical procedure; and

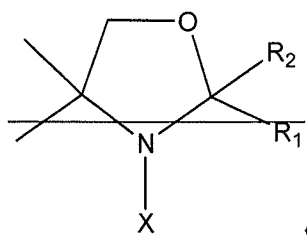
administering to the patient after the performing step, an additional amount of a ~~nitroxide~~ 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl effective to reduce a harmful effect of ischemia;

~~wherein the nitroxide is selected from the group consisting of~~



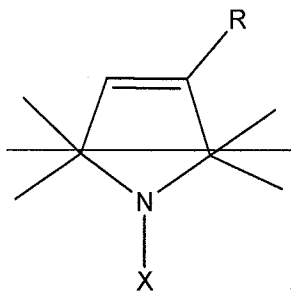
~~or a pharmaceutically acceptable salt thereof~~

~~wherein X is selected from O• and OH, and R is selected from COOH, CONH, CN, and CH<sub>2</sub>NH<sub>2</sub>,~~



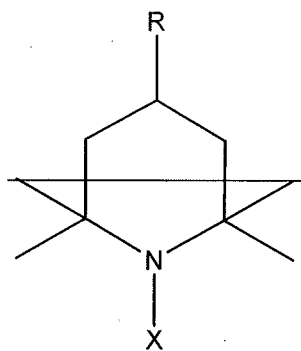
or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH, and R<sub>1</sub> is selected from CH<sub>3</sub> and spirocyclohexyl, and R<sub>2</sub> is selected from C<sub>2</sub>H<sub>5</sub> and spirocyclohexyl;



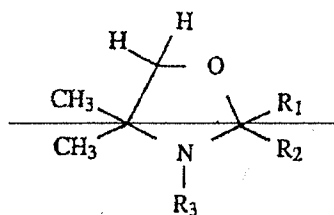
or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH and R is CONH<sub>2</sub>;

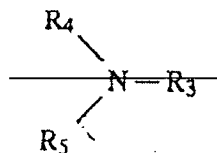


or a pharmaceutically acceptable salt thereof

wherein X is selected from O• and OH and R is selected from H, OH, and NH<sub>2</sub>;



wherein  $R_1$  is  $CH_3$ ;  $R_2$  is  $C_2H_5$ ,  $C_3H_7$ ,  $C_4H_9$ ,  $C_5H_{11}$ ,  $C_6H_{13}$ ,  $CH_2-CH(CH_3)_2$ ,  $-CHCH_2C_2H_5$ , or  $(CH_2)_7-CH_3$ , or wherein  $R_1$  and  $R_2$  together form spirocyclopentane, spirocyclohexane, spirocycloheptane, spirocyclooctane, 5-cholestane, or norbornane;  $R_3$  is  $O$  or  $OH$ , or a physiologically acceptable salt thereof which has antioxidant activity;



wherein  $R_3$  is  $O$  or  $OH$ ; and

wherein  $R_4$  and  $R_5$  combine together with the nitrogen to form a heterocyclic group; wherein the atoms in the heterocyclic group (other than the N atom shown in the formula) may be all C atoms or may be C atoms and one or more N, O and/or S atoms; or

wherein  $R_4$  and  $R_5$  combine together to form substituted or unsubstituted pyrrole, imidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, pyridine, pyrimidine, or purine; or

wherein  $R_4$  and  $R_5$  themselves comprise a substituted or unsubstituted cyclic or heterocyclic group;

2-ethyl 2,5,5-trimethyl 3-oxazolidine-1-oxyl, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), 4-hydroxy 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPOL), 4-amino-2,2,6,6-tetramethyl-1-piperidinyloxy (Tempamine), 3-Aminomethyl PROXYL, 3-Cyano-PROXYL, 3-Carbamoyl-PROXYL, 3-Carboxy-PROXYL, 4-oxo-TEMPO, 4-amino-TEMPO, 4-(2-bromoacetamido)-TEMPO, 4-(ethoxyfluorophosphonyloxy)-TEMPO, 4-hydroxy-TEMPO, 4-(2-iodoacetamido)-TEMPO, 4-isothiocyanato-TEMPO, 4-maleimido-TEMPO, 4-(4-nitrobenzoyloxy)-TEMPO, and 4-phosphonoxy-TEMPO.

**Application No.:** 10/554,299  
**Filing Date:** September 22, 2006

43. (Canceled) The method of Claim 42, wherein the nitroxide is 4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl.

44. (Previously Presented) The method of Claim 42, wherein the medical procedure is the treatment of a hemorrhage.

45. (Previously Presented) The method of Claim 42, wherein the medical procedure is the treatment of an aneurysm.

46. (Previously Presented) The method of Claim 42, wherein the medical procedure is surgery.

47. (Previously Presented) The method of Claim 42, wherein the medical procedure is an endovascular procedure.